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PRE-APPEAL BRIEF REQUEST FOR REVIEW	Docket Number (Optional) 1422-0619P	
	Application Number 10/743,740-Conf #9686	Filed December 24, 2003
	First Named Inventor Eiichi IISHI et al	
	Art Unit 1624	Examiner K. Habte

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s)
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant /inventor
- [ ] assignee of record of the entire interest. See 37 CFR 3.71 Statement under 37 CFR 3 73(b) is enclosed (Form PTO/SB/96)
- [x] attorney or agent of record
  Registration number 28,977
- [ ] attorney or agent acting under 37 CFR 1 34
  Registration number if acting under 37 CFR 1 34 _____


Signature

for

Gerald M. Murphy, Jr.
Typed or printed name

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February 16, 2007
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required
Submit multiple forms if more than one signature is required, see below*

- [ ] *Total of 1 forms are submitted

Docket No.: 1422-0619P
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Eiichi IISHI et al.

Application No.: 10/743,740 Confirmation No.: 9686

Filed: December 24, 2003 Art Unit: 1624

For: ANHYDROUS MIRTAZAPINE CRYSTALS AND PROCESS FOR PREPARING THE SAME Examiner: K. Habte

REQUEST FOR PRE-APPEAL BRIEF CONFERENCE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the final Office Action mailed October 19, 2006, the appellant respectfully requests a pre-appeal brief conference. This request is being filed concurrently with a Notice of Appeal.

REMARKS

Applicant requests withdrawal of the rejection of record as being clearly erroneous in fact and in law for the reasons set forth below.

Single Ground Of Rejection To Be Reviewed

Claims 1-6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kaspersen et al. (Journal of Label. Comp. and Radiopharm., 27, No. 9, 1055, 1989). Applicants respectfully traverse the rejection.

Applicants believe that claims 5-6 are patentable over Kaspersen et al. and now discuss the patentable distinctions between claims 5-6 and the teachings of Kaspersen et al. Applicants will discuss the patentable distinctions of claims 1-4 over Kaspersen et al separately below.

Instant claims 5-6

Throughout prosecution, the Examiner has relied upon the experimental workup of compound 1c (in the paragraph bridging pages 1065-1066 of Kaspersen et al.) for anticipating the instantly claimed invention based upon a theory of inherency, i.e., that the ^{13}C labeled mirtazapine compound 1c is inherently formed into crystals having **(i)** a water content of not more than 0.5% by weight and **(ii)** a hygroscopic degree of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours, as presently claimed. However, instant claims 5 and 6 each recite a feature of the mirtazapine product which is distinct from an *explicitly* recited property of the compound 1c, and that is the melting point. Instant claims 5 and 6 recite that the mirtazapine crystals have a melting point of **114-116°C.** This is in distinction to the teachings of Kaspersen et al. which recite that the melting point of the mirtazapine product 1c is **123.8-125.8°C**.

As the MPEP directs, all the claim limitations must be taught or suggested by the prior art to establish a *prima facie* case of anticipation. See MPEP §2131. In view of the fact that Kaspersen et al. do not teach (explicitly or implicitly) or suggest mirtazapine crystals having a melting point of **114-116°C**, as presently claimed, a *prima facie* case of anticipation cannot be said to exist.

In the October 19, 2006 Office Action, the Examiner has commented on the melting point discrepancy between the mirtazapine crystal of Kaspersen et al. and the melting point described in claims 5 and 6. Specifically, instant claims 5 and 6 recite that the melting point of the crystals is 114-116 °C whereas Kaspersen et al. teach that the mirtazapine product has a melting point of 123.8-125.8 °C. The Examiner notes this difference but has stated that the "*melting difference could arise from impurities in the product. It could also arise from human error or instrumentation error.*" (Emphasis added).

Applicants respectfully disagree with the Examiner's comments. First, Applicants agree with the Examiner that a melting point can change when impurities are present in the crystalline

structure. However, claims 5 and 6 exclude these impurities by reciting the melting point range of 114-116 °C which is sharp and differs from the melting point range of Kaspersen et al by at least 7.8°C (123.8-116).

Second, with respect to the Examiner' assertion that the difference in the melting point could be from human error or instrumentation error, it is Applicants' position that the Examiner must take the description of Kaspersen et al. as being true unless there is some other valid reason to suspect that the description is false. The article to Kaspersen et al. made it through peer review and appears in a respected journal, i.e., the Journal of Labelled Compounds and Radiopharmaceuticals.

Furthermore, this line of reasoning used by the Examiner is a slippery slope which is frowned upon by the patent office. MPEP 2121 states that a prior art reference is presumed to be operable and enabling. The burden is on Applicants to show otherwise. In the instant case, Applicants are confused as to what the Examiner wants Applicants to do in response to the Examiner's assertion that the melting point described in Kaspersen et al. is incorrect. The Examiner appears to be putting the burden on Applicants to prove that the reference is operable, i.e., that the melting point is actually 123.8-125.8 °C as described by Kaspersen et al. Could this be what the Examiner wants? Nevertheless, without a valid reason given by the Examiner as to why Kaspersen et al. were able to make it through peer review with incorrect information, it is proper to assume that the melting point of Kaspersen et al. is correct.

As such, there is a clear distinction between the teachings of Kaspersen et al. and the invention as described in instant claims 5-6. Accordingly, withdrawal of the rejection to the extent that it applies to claims 5-6 is respectfully requested.

Instant claims 1-4

The Examiner has maintained the position that Applicants are required to repeat the experiments of Kaspersen et al. to show that the mirtazapine crystals of Kaspersen et al. do not have the presently claimed properties: **(i)** a water content of not more than 0.5% by weight and **(ii)** a hygroscopic degree of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours, as presently claimed. However, it is Applicants' position that Example 8 in the present

specification is sufficiently close to the description of Kaspersen et al., so that the skilled artisan would come to the reasonable conclusion that the mirtazapine crystals of Kaspersen et al. do not have the presently claimed properties **(i)** and **(ii)**, especially property **(i)**.

The workup of Kaspersen et al. is compared to Example 8 of the present specification in the following table:

Workup of 1c of Kaspersen et al.	**Example 8 of the present specification**
The product was extracted with ethyl acetate, dried over Na_2SO_4 and evaporated to dryness to yield 950 mg (85%) of crude 1c. The crude 1c was purified by chromatography over Alox B (eluted with hexane/ethyl acetate 7:3, v/v) to yield 830 mg. For the final purification the product was treated twice with 100 mg of charcoal in n-hexane (containing 1% of methanol) followed by crystallization from methanol/water (1:1, v/v) yielding 600 mg (53%) Org 3770 as colourless crystals, m.p. 123,8-125,8 °C. No impurities were detectable either on TLC, HPLC or GC.	In 4728 g of methanol was dissolved 1195.46 g of a crude mirtazapine (HPLC purity: 99.0%) at 0° to 5°C., and 12 g of decolorizing carbon was added thereto, and the mixture was stirred at 5°C. for 15 minutes. This solution was filtered at 0° to 5°C. Thereafter, 4065 g of ion-exchanged water was introduced into the filtrate, and 100 mg of seed crystals were added thereto. Thereto was added in a thin stream 9707 g of ion-exchanged water at 0° to 10°C. to allow crystallization. The mixture was stirred at 0° to 5°C. for 1 hour, and crystals were filtered. The crystals were washed with a mixed solution (liquid temperature: 0° to 5°C.) of 340 g of methanol and 1291 g of ion-exchanged water. The crystals were dried under reduced pressure (4 to 5.3 kPa) at 50° to 60°C. so that the water content was attained to not more than 3.5% by weight.

In view of the fact that Kaspersen et al. is silent with respect to the drying conditions, it is Applicants' position that the crystals of Kaspersen et al. would be dried under "ordinary conditions" such as those used in Example 8 of the present specification. The Examiner has agreed in the August 28, 2006 Interview that the process of Kaspersen et al. uses "ordinary drying conditions" as is described in Example 8 in the present specification.

Furthermore, the Examiner will note that Example 8 of the present application and the invention of Kaspersen et al. are the same in that mirtazapine is recrystallized from a solvent mixture of methanol/water. In view of these similarities, it is appropriate for the Examiner to rely on the experimental data of Example 8 in the present specification to show that the mirtazapine

crystals of Kaspersen et al. do not have the presently claimed property **(i)** a water content of not more than 0.5% by weight.

The Examiner's attention is now directed to Example 7 (as a nonlimiting embodiment) of the present specification as an example which shows the type of conditions needed to obtain **(i)** a water content of not more than 0.5% by weight, as presently claimed. In Example 7, the crystals of mirtazapine hemihydrate obtained in Example 6 were dried at 90° to 95°C under reduced pressure of 1330 to 1862 Pa. The resulting water content was found to be 0.1% by weight.

The product of Example 8, dried under ordinary conditions, has a water content of about 3.5 % by weight, which is outside the inventive range of water content of "not more than 0.5% by weight". Since the product of Kaspersen et al. is also dried under ordinary conditions, it follows that the product of Kaspersen et al. has a water content of about 3.5 % by weight. Thus, Example 8 of the present specification is relevant to show that it is reasonable to conclude that the product of Kaspersen et al. is outside the inventive range of water content of "not more than 0.5% by weight".

Based on the foregoing, Kaspersen et al. does not teach a mirtazapine crystal which inherently has the presently claimed properties **(i)** and **(ii)**, and as such, withdrawal of the anticipation rejection is respectfully requested.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: February 16, 2007

Respectfully submitted,

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